

## Report

# Daytime Light Exposure Dynamically Enhances Brain Responses

Gilles Vandewalle,<sup>1</sup> Evelyne Balteau,<sup>1</sup>  
Christophe Phillips,<sup>1</sup> Christian Degueldre,<sup>1</sup>  
Vincent Moreau,<sup>2</sup> Virginie Sterpenich,<sup>1</sup>  
Geneviève Albouy,<sup>1</sup> Annabelle Darsaud,<sup>1</sup>  
Martin Desseilles,<sup>1,3</sup> Thien Thanh Dang-Vu,<sup>1,4</sup>  
Philippe Peigneux,<sup>1</sup> André Luxen,<sup>1</sup> Derk-Jan Dijk,<sup>5</sup>  
and Pierre Maquet<sup>1,4,\*</sup>

<sup>1</sup>Cyclotron Research Center

<sup>2</sup>Department of Physics

University of Liège

Liège B-4000

Belgium

<sup>3</sup>Department of Psychiatry

<sup>4</sup>Department of Neurology

Centre Hospitalier Universitaire

Liège B-4000

Belgium

<sup>5</sup>Surrey Sleep Research Centre

University of Surrey

Guildford GU2 7XP

United Kingdom

## Summary

In humans, light enhances both alertness and performance during nighttime and daytime [1–4] and influences regional brain function [5]. These effects do not correspond to classical visual responses but involve a non-image forming (NIF) system, which elicits greater endocrine, physiological, neurophysiological, and behavioral responses to shorter light wavelengths than to wavelengths geared toward the visual system [6–11]. During daytime, the neural changes induced by light exposure, and their time courses, are largely unknown. With functional magnetic resonance imaging (fMRI), we characterized the neural correlates of the alerting effect of daytime light by assessing the responses to an auditory oddball task [12–15], before and after a short exposure to a bright white light. Light-induced improvement in subjective alertness was linearly related to responses in the posterior thalamus. In addition, light enhanced responses in a set of cortical areas supporting attentional oddball effects, and it prevented decreases of activity otherwise observed during continuous darkness. Responses to light were remarkably dynamic. They declined within minutes after the end of the light stimulus, following various region-specific time courses. These findings suggest that light can modulate activity of subcortical structures involved in alertness, thereby dynamically promoting cortical activity in networks involved in ongoing nonvisual cognitive processes.

## Results and Discussion

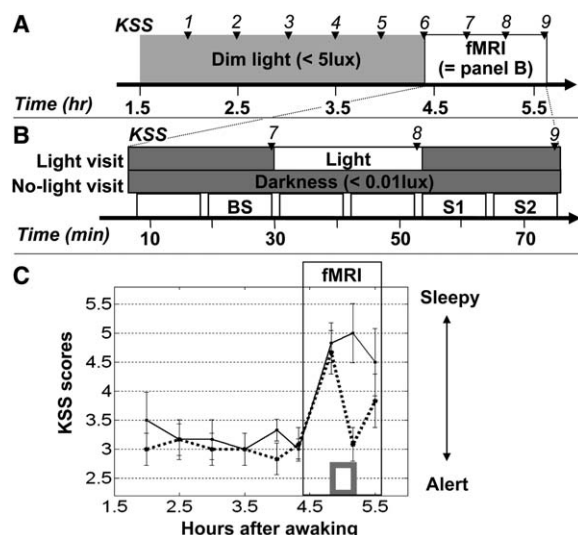
Subjects were scanned during six consecutive 8 min sessions during which they performed an auditory oddball task (Figures 1A and 1B). This task is devoid of any visual processing and elicits reproducible brain responses [12]. Data were acquired before (two sessions; <0.01 lux), during (two sessions;  $>4.16 \times 10^{15}$  photons/cm<sup>2</sup>/s or >7000 lux), and after (two sessions; <0.01 lux) one eye was exposed for 21 min to a bright white light (spectrum: Figure S1 in the Supplemental Data available online). Light exposure occurred approximately 5 hr after habitual wake-up time. The same protocol was followed on another day, but no light was administered. The order of the day with and without light was counterbalanced over subjects.

Only data acquired in three sessions of darkness (hereafter referred to as baseline and first and second postlight sessions) were considered. Data obtained during sessions with light exposure were discarded because they were contaminated by classical visual responses [16]. The very first session was not used because it can be contaminated by physiological events related to recent postural changes [17]. During nighttime, melatonin suppression is often used to ensure that light exposure elicits a non-image forming (NIF) response. In our case, because melatonin level is already very low during daytime [18], we relied on the known alerting effect of light [1–3, 8], as assessed by the Karolinska Sleepiness Scale (KSS) [19], to ascertain an effect of light.

The time frame of the NIF light-related effects was examined at two levels in subjects showing an alerting effect of light ( $n = 12$ , Supplemental Data). First, we report modulation of evoked responses by light exposure; this modulation is expressed between sessions preceding (baseline session) and following (postexposure sessions 1 and 2) the illumination. Second, we addressed light-dependent modulations of the evoked responses within sessions, over a shorter time scale. The light-dependent effect here was the time-dependent adaptation of evoked responses within each session. Finally, to establish the relationship between these light-dependent effects and the alerting effects of light exposure, we extended the cohort to include nonresponders (people who did not exhibit an alerting effect of light) and used a subject-specific measure of this alerting effect to predict the light-dependent effects described above.

The first set of analyses included subjects showing an alerting effect of light. As expected, repeated-measures ANOVA on KSS scores revealed a main effect of session [ $F(8,88) = 6.19$ ;  $p < 0.00001$ ], a main effect of day [ $F(1,11) = 5.60$ ;  $p = 0.037$ ], and a day by session interaction [ $F(8,88) = 4.30$ ;  $p = 0.00021$ ; Figure 1C]. Planned comparisons showed significant differences between days in KSS scores only for the measure collected at the end of the illumination period [ $F(1,11) = 19.51$ ;  $p = 0.001$ ; other measures:  $F(1,11) < 3.5$ ;  $p > 0.08$ ].

\*Correspondence: [pmaquet@ulg.ac.be](mailto:pmaquet@ulg.ac.be)



**Figure 1.** Experimental Design and Subjective Alertness Evolution (A) General timeline relative to scheduled wake time (hr). Arrows indicate KSS 1–9. (B) Timeline of the fMRI acquisition of both days (enlarged fMRI box of panel [A]). Empty rectangle depicts six oddball sessions. BS indicates baseline session; S1 and S2 indicate postexposure sessions 1 and 2. Time is in minutes after entering the scanner. Arrows indicate KSS 7–9. (C) Mean subjective alertness of subjects ( $\pm$  standard error of the mean [SEM]). The solid line is for the day without light exposure. The dotted line is for the day with light exposure. The gray rectangle indicates the light exposure period. The empty rectangle indicates the fMRI period. Time is relative to scheduled wake time (hr).

In partially sleep-deprived subjects, daytime white-light exposure has been reported to improve reaction times [3]. In contrast, our normally rested subjects were able to maintain steady reaction times during all sessions (Supplemental Data), despite concurrent fluctuations in alertness. Differences in cognitive task, sleep pressure, and exposure duration probably explain this discrepancy. Moreover, different NIF responses might be sensitive to different wavelengths, as suggested with subjective alertness [20].

For functional magnetic resonance imaging (fMRI) data, a significant day (light > no-light) by session (post 1 > baseline) interaction effect was observed in the left hippocampus ( $-30 -30 -2$  mm;  $Z = 3.91$ ;  $p_{\text{svc}} = 0.011$ ), right anterior cingulate cortex ( $10 36 12$  mm;  $Z = 3.88$ ;  $p_{\text{svc}} = 0.011$ ), left precuneus ( $-8 -50 72$  mm;  $Z = 3.82$ ;  $p_{\text{svc}} = 0.014$ ), and right intraparietal sulcus (rIPS;  $22 -56 40$  mm;  $Z = 3.33$ ;  $p_{\text{svc}} = 0.049$ ; Figures 2A–2D; Table S1). Mean parameter estimates showed that in these areas, light exposure prevented the progressive decline in responses observed in continuous darkness during the day without light and increased activity as compared to baseline.

In the postexposure period, a significant day by session (post 1 > post 2) interaction was observed in the right precuneus ( $8 -54 52$  mm;  $Z = 3.67$ ;  $p_{\text{svc}} = 0.036$ ) and right superior temporal gyrus (rSTG;  $44 -16 -2$  mm;  $Z = 3.25$ ;  $p_{\text{svc}} = 0.038$ ; Figures 2E and 2F; Table S2). Mean parameter estimates showed that the responses in these regions decreased from the first to the second postexposure session of the day with light

exposure, whereas during the day without light exposure, responses increased from the first to the second postexposure session (this latter increase did not rule the interaction effect; Supplemental Data). No significant modulation had been found in the previous day by session (post 1 > baseline) interaction in the rSTG and right precuneus. This may be due to the lack of statistical power of between-session contrasts at the random-effects level. In keeping with this suggestion, posterior probabilities of activation [21] were considerably larger during the first postexposure session of the day with light exposure in both regions (precuneus:  $p_{\text{light}} = 0.47$ ,  $p_{\text{no-light}} = 0.01$ ; rSTG:  $p_{\text{light}} = 0.81$ ,  $p_{\text{no-light}} = 0.05$ ).

Importantly, no significant increase in response was observed in the second postexposure session ( $p_{\text{uncorrected}} < 0.001$ ; Table S3). These findings suggest that the effects of light exposure largely dissipate within 10 min after the end of the light exposure, similarly to alertness, which was only transiently enhanced by light exposure. Finally, no decrease in brain response was elicited by light exposure.

We then looked for brain areas in which responses would dynamically dissipate within sessions. Such changes would not necessarily give rise to significant changes in activity when averaged over a whole session and would not appear in between-session contrasts. We therefore compared the within-session temporal modulations of brain responses in postexposure sessions to baseline. Within the set of areas where a significant temporal modulation was detected, we considered only regions in which mean parameter estimates were consistent with an effect of light counteracting the decrease in activity induced by continuous darkness (Figure 3, lower panels). In these conditions, any negative modulation of activity by time can arguably be interpreted as a dissipation of the effects following light exposure (Tables S4 and S5).

The day by session (post 1 > baseline) interaction computed on brain responses modulated by time identified five regions (Figure 3): the right insula ( $40 20 8$  mm;  $Z = 4.48$ ;  $p_{\text{svc}} = 0.002$ ), right posterior cingulate cortex ( $8 -26 42$  mm;  $Z = 3.35$ ;  $p_{\text{svc}} = 0.049$ ), right superior parietal lobe (rSPL;  $14 -44 76$  mm;  $Z = 4.23$ ;  $p_{\text{svc}} = 0.007$ ), right dorso-lateral prefrontal cortex (rDLPFC;  $28 12 42$  mm;  $Z = 3.50$ ;  $p_{\text{svc}} = 0.046$ ), and right fusiform gyrus ( $34 -84 -16$  mm;  $Z = 3.99$ ;  $p_{\text{svc}} = 0.009$ ). In all these regions, responses decreased more quickly after light exposure than during continuous darkness, as compared to baseline. The computed temporal modulation (Figure 3, middle panels) shows that responses were never maintained at initial postlight levels for more than 50 scans ( $\sim 100$  s). A similar temporal modulation was identified, again in the right insula ( $40 18 6$  mm;  $Z = 3.71$ ;  $p_{\text{svc}} = 0.019$ ), by the day by session (post 2 > baseline) interaction (Figure 3A, dotted line). These results indicate that the dissipation of the responses to light exposure follows multiple region-specific time courses.

The oddball task engages cognitive processes such as auditory perception, attention, and working memory [13–15]. Light modulated responses in the right SPL, DLPFC, and IPS, each part of the top-down attention network, and in the right insula, anterior cingulate, and STG, each involved in the bottom-up reorientation of attention toward low-frequency events [15, 22]. Light also

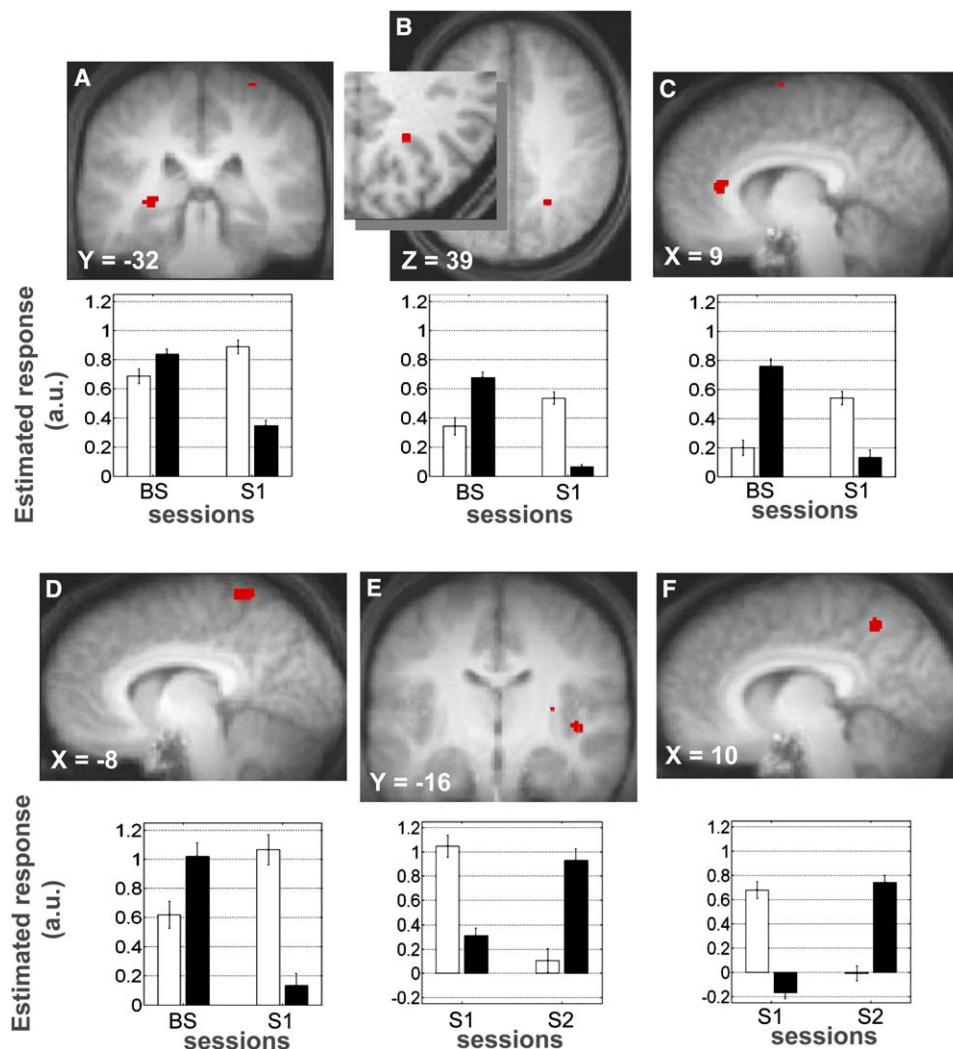


Figure 2. Day by Session Interactions

Graphs show mean parameter estimates of the day with light exposure (empty bars) and without light exposure (filled bars) (arbitrary units  $\pm$  SEM). BS indicates baseline session; S1 and S2 indicate postexposure sessions 1 and 2.

(A–D) Day by session (post 1 > baseline) interactions. (A) Left hippocampus. (B) rIPS (inset: enlarged parietal region in a representative subject). (C) Right anterior cingulate. (D) Left precuneus.

(E and F) Day by session (post 2 > baseline) interactions. (E) rSTG. (F) Right precuneus.

In all figures, statistical results are overlaid to the population mean structural image ( $p_{\text{uncorrected}} < 0.001$ ).

induced changes in the left hippocampus, involved in perception, identification, and integration of the stimulus, processes in which the superior temporal sulcus and rIPS are also involved [14, 15, 23]. The fusiform gyrus, precuneus, and posterior cingulate cortex are typically reported in oddball fMRI, and their responses were also modulated by light [13, 14, 24].

In our final analysis, we extended our cohort to cover people who did not show an alerting response to light. Their reaction times were reliably faster than those of responders (Supplemental Data), suggesting that they remained very alert at all times and no effect of light on alertness could possibly be observed. We therefore wanted to establish the relationship between the light-dependent modulation of evoked responses and variation of alertness at the between-subject level. To summarize alertness variations, we used the principal

eigenvariate (following a principal component analysis of the KSS scores). This eigenvariate is a scalar summary of the degree to which each subject follows the course of the principal eigenvector, which accounted for 68.49% of alertness variance (inset Figure 4A).

Responses identified in the day by session (post 1 > baseline) interaction were significantly related to the first eigenvariate in a single area of the thalamus, in a location compatible with the pulvinar ( $-2 -24 8$  mm;  $Z = 4.11$ ;  $p_{\text{svc}} = 0.003$ ; Figure 4B and Table S6), an area distinct from the brain regions reported in the other analyses. The thalamus, a key structure modulating alertness, is involved in the interaction between alertness and attention in humans [25, 26]. This result indicates that the change in thalamic response to odd tones after light exposure is linearly related to alertness variation induced by light exposure, independently of whether light

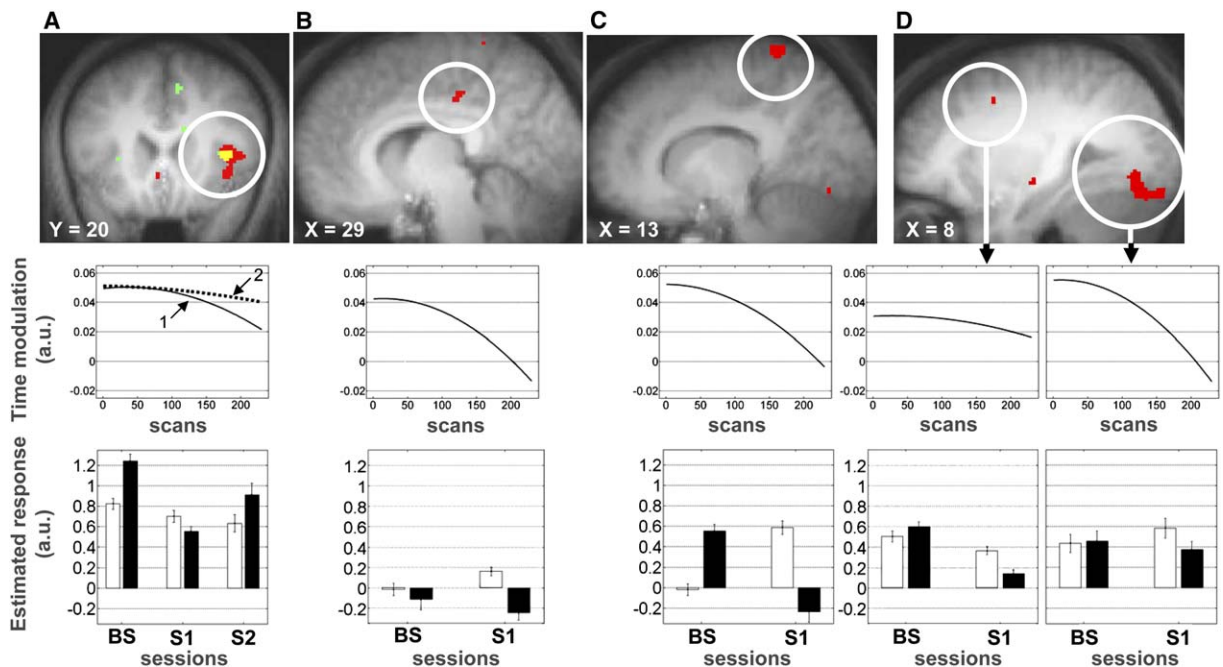


Figure 3. Day by Session Interaction Computed on the Brain Responses Modulated by Time

Upper panels show day by session (post 1 > baseline) interactions (red voxels). (A) also shows light condition by session (post 2 > baseline) interactions in green (yellow for overlapping voxels). (A) Right insula. (B) Right posterior cingulate. (C) rSPL. (D) rDLPFC (left) and right fusiform gyrus (right).

Middle panels show reconstruction of the modulation of the response in the first postexposure session of the day with light exposure (arbitrary units) over the course of 230 scans (~8 min). In (A), the dotted line pertains to the second postexposure session. Temporal modulation of the BOLD response was reconstructed by the sum of both time modulators weighted by their respective mean parameter estimates.

Lower panels show mean parameter estimates in the baseline (BS) and first postexposure (S1) sessions, and second postexposure session (S2) for (A), of the days with light (empty bars) and without light exposure (filled bars) (arbitrary units  $\pm$  SEM).

induced a behavioral effect in every subject. Because of this alerting effect, responses to the cognitive challenge are increased at the cortical level.

Besides the classical visual system, irradiance information is interpreted in mammals by a NIF system [27] that generates a wide range of physiological responses, such as the modulation of alertness [1, 2, 8], hormone secretion [2, 8, 18], heart rate, sleep latency, core body temperature [1, 2, 8, 18], retina neurophysiology [7], pupillary constriction [28], and gene expression in the SCN [29].

The light-induced modulations of brain responses to odd-tone detection arguably represent still another type of NIF response. It is unlikely that the classical visual system might interfere with a pure auditory task and modulate the responses elicited by the detection

of odd tones, presented in a stream of frequent tones, after the light exposure has ended. In addition, the light-induced modulation of brain responses presents two basic features of NIF responses: They are induced by, and they outlast, light exposure. Classical visual responses to light typically cease very shortly after the end of the stimulation. Even in the retina, cones or rods respond to light stimulation in a stimulus-locked manner. In contrast, light pulses of a few seconds induce a sustained response that outlasts the light stimulus and declines slowly in melanopsin-expressing ganglion cells, photoreceptors in the NIF system [30]. Both classical and nonclassical photoreceptors contribute to NIF response in rodents [31]. Because the white-light source covered the whole visible spectrum and included ~3 times more photons in the photopic than in the NIF

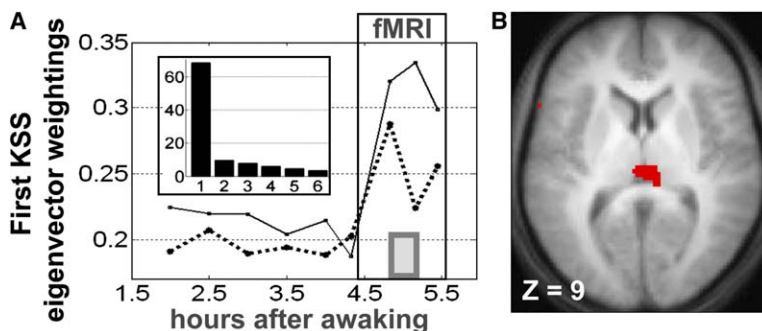


Figure 4. Interaction of Light and Alertness

(A) Profile of the first eigenvector of the singular value decomposition on KSS scores. The solid line is for the day without light exposure. The dotted line is for the day with light exposure. The inset shows percentage of variance explained by the six first components.

(B) Day by session (post 1 > baseline) interaction related to the first eigenvector in the pulvinar.



range, classical and melanopsin photoreceptor were differentially stimulated [27]. However, we cannot determine the relative contribution of each type of photoreceptors to the brain-response modulation.

The present results confirm and extend our previous positron emission tomography (PET) results. First, this fMRI study shows that short white-light exposure affects brain function also during daytime. Second, event-related fMRI characterizes transient cerebral responses to a cognitive challenge [32], which implies that only areas involved in odd-tone detection could be identified, whereas PET characterized enduring light-induced changes in functional states of the brain, related or not to the ongoing task. Third, fMRI, because of its better temporal and spatial resolutions, allowed us to show that light exposure elicits effects on brain activity that quickly dissipate following region-specific time courses. Although the topography of brain responses depends on the task executed by the participants, the multiple dynamics of the light-induced modulations in regional brain responses might represent a general phenomenon.

Melanopsin-expressing ganglion cells project to several hypothalamic regions, including the SCN [33]. In rodents, indirect projections from the SCN to cell groups involved in arousal regulation exist in the forebrain and brainstem [34, 35]. At present, it is not known which of these projections contribute to the establishment of a cortical response to light exposure. It is likely that the initial NIF responses activate brainstem and/or diencephalic structures, which in turn modulate thalamic, then cortical, responses. The direct projections of the melanopsin retinal ganglion cells to the lateral geniculate body [30], if also present in humans, might also be the natural pathways followed by irradiance information to influence thalamic and, indirectly, cortical activity.

## Conclusions

A short exposure to bright light can transiently prevent the sleepiness developed in continuous darkness. At the macroscopic systems level, the alerting effect of light is reflected by an enhanced thalamic activity, which in turn might modulate cortical responses to a cognitive challenge, independently from any visual information. The enhanced brain responses outlast the exposure but quickly dissipate following regionally specific time courses.

## Experimental Procedures

### Subjects

Healthy participants ( $n = 19$ ; age: 20–25) gave written informed consent and followed a constant sleep schedule, assessed by using wrist actigraphy (Cambridge Neurosciences, United Kingdom), for 7 days before the first experiment day and until the second, 2 days later. During each experiment day, subjects first stayed in dim light (<5 lux) for 3 hr during which they rated their vigilance on the KSS every 30 min. Three additional KSS scores were obtained right before the light exposure, at the end of it, and at the end of the experiment. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège.

### Oddball Task

Stimuli (300/session) consisted of frequent (600 Hz) and odd tones (400 Hz), presented ~90% and ~10% of the time in a pseudo-randomized order.

### Light Exposure

The exposed eye was counterbalanced. Light was transmitted by an optic fiber from a source (PL900, Dolan-Jenner, Massachusetts) to a diffuser ensuring uniform illumination.

### Demographic Data

Three subjects did not conform to the instructions requiring a response as fast as possible and were excluded. We relied on the known alerting effect of light [1–3, 8] to ascertain an effect of light. Subjects were considered to be responders if, when subtracting the KSS score obtained right before light exposure period from the KSS score obtained at the end of it, the score of the day with light exposure was larger than the score of the day without light exposure. Twelve responders were included in the analysis looking for the effects of light exposure. The analysis testing the effects of light on the correlates of alertness incorporated four additional nonresponders.

### Data Analysis and fMRI Scan Acquisition

fMRI data were acquired with a 3T MR scanner (Allegra, Siemens, Germany). Functional volumes were analyzed with SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>). They were corrected for head motion, spatially normalized, and smoothed. Analysis was conducted in two serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated with a general linear model in which activity evoked by odd tones in each session was modeled by stick functions, convolved with a canonical hemodynamic response function. Two further regressors represented the modulation of brain responses to odd tones by linear and quadratic functions of time. Movement parameters were included as covariates of no interest. Low-frequency drifts were removed by using high-pass filtering with a cut-off period of 128 s. Serial correlations in fMRI signal were estimated with an autoregressive (order 1) plus white noise model and a restricted maximum-likelihood algorithm. Summary statistic images resulting from linear contrasts were smoothed and entered in a second-level analysis accounting for intersubject variance in the main effects of light and corresponding to a one-sample *t* test for brain responses to odd tones. Time modulators were included in a separate parametric within-subject one-way ANOVA, for which error covariance was not assumed independent between regressors and correction for nonsphericity was used for final inferences [36]. The resulting set of voxel values for each contrast constituted maps of the *T* statistics for the main responses and *F* statistics when they were modulated by time, thresholded at  $p = 0.001$ . The second analysis, testing for the effects of light on alertness, used a singular value decomposition conducted on KSS scores of both days (18 values) collected over all subjects ( $n = 16$ ). The eigenvectors related to the highest eigenvalue were selected for the analysis. The corresponding eigenvector over subjects was used in a regression at the random-effects level, on the contrast images representing the day by session (post 1 > baseline) interaction. All statistical inferences were performed after correction for multiple comparisons on small spherical volumes (svc) at  $p_{svc} < 0.05$  threshold, around a priori locations of activation taken from published work on attention, arousal regulation, and oddball tasks in fMRI.

### Supplemental Data

Supplemental Data include Supplemental Results, Supplemental Experimental Procedures, one figure, and six tables and are available with this article online at: <http://www.current-biology.com/cgi/content/full/16/16/1616/DC1/>.

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